Exhibit A

STABILITY

STABILITY SUMMARY AND CONCLUSIONS

Studies Conducted

1) Long-term and accelerated stability

Four batches of Clozapine 50 mg/ml Suspension have been placed onto the stability program as outlined below.

Table 1: Clozapine 50 mg/ml Suspension undergoing Stability Testing

Packed Batch Number	Site of Manufacture	Batch Size (L)	Batch Size (units)	Registration/ Commercial	Orientation	Date of manufacture	Date of Study commencement
17298	Douglas	250	2500	Registration	Upright	Dec 2004	Jan 2005
17359	Douglas	250	2500	Registration	Upright	Dec 2004	Jan 2005
17361	Douglas	250	2500	Registration	Upright	Dec 2004	Jan 2005
17361	Douglas	250	2500	Registration	Inverted	Dec 2004	Jan 2005
23283	Douglas	1000	10000	Commercial	Upright	Apr 2007	Jun 2007
23283	Douglas	1000	10000	Commercial	Inverted	Apr 2007	Jun 2007
32126	Douglas	1000	10000	Commercial	Upright	Oct 2008	Dec 2008

Batches 17298, 17359 and 17361 were the registration batches. Batches 23283 and 32126 are the commercial batches that have been scaled up to 1000 L.

All five batches of Clozapine 50 mg/ml Suspension were packed in amber glass bottles (type 3) fitted with child resistant, tamper evident caps.

The available stability data for Clozapine 50 mg/ml is summarised below.

Table 2 : Clozapine 50 mg/ml Suspension Stability Data Available

Batches Studied	Orientation	25 °C/60 % RH Available results (months)	40 °C/75 % RH Available results (months)
17298	Upright	0-3-6-9-12-18-24	0-3-6
17359	Upright	0-3-6-9-12-18-24	0-3-6
17361	Upright	0-3-6-9-12-18-24	0-3-6
17361	Inverted	0-3-6-9-12-18-24	0-3-6
23283	Upright	0-3-6-9-12-18-24	0-3-6
23283	Inverted	0-3-6-9-12-18-24	0-3-6
32126	Upright	0-3-6-9-12	0-3-6

The batches currently undergoing stability testing will continue to be tested at the conditions and time points summarised in the following table.

Table 3: Stability Protocol

Time Point (months)	25 °C/60 % RH	30 °C/65 % RH	40 °C/75 % RH
Initial	✓ (M)	☒ (M)	✓ (M)
3	✓	☒	✓
6	✓	☒	✓ (M)
9	✓	☒	
12	✓	☒ (M)	
18	✓		
24	✓ (M)		
36	✓ (M)		

✓ = Tested at this time point
(M) = Microbial limits to be tested at this time point
☒ = Tested on demand

Characteristics Studied

The characteristics studied are according to the current shelf life specification for Clozapine 50 mg/ml Suspension at the time of testing. Tests include:

Physical Characteristics

- Description
- Viscosity

Chemical characteristics

- pH
- Related Substances
- Assay:
  - Clozapine
  - Methyl paraben sodium
  - Propyl paraben sodium
- Dissolution[1]

Other tests

- Microbial Limits:
  - Total Viable Aerobic Count
  - Fungi (Yeasts and Moulds)
  - E.coli

Limits for these tests are located in the Shelf Life Specifications, presented in Appendix 1.

[1] Dissolution to be performed at 12 M, 24 M and 36 M time-points on future batches placed on stability

Summary of Results

Tabular summaries of the results are located in Appendix 2.

Description

The physical appearance for all batches of Clozapine Suspension (upright and inverted) was unaffected by storage under the different stability conditions over the time period studied.

Viscosity

For both the registration batches (250 L) and the commercial batches (1000 L), the viscosity of all batches of Clozapine Suspension (upright and inverted) remained well within the specifications when stored for up to 24-months at 25 °C/60 % RH and for six months at 40 °C/75 % RH.

For the registration batches it was noted that in batch 17298 stored for six months at 40 °C/75 % RH an uncharacteristically high viscosity result was observed (2536 cps) when compared to the previous time-point (2125 cps) and to the other batches 17359 (2043 cps), 17361 (inverted; 2098 cps) and 17361 (upright; 2122 cps) also stored at this station. In addition, after 18 months storage at 25°C/60 % RH of the same batch (17298), a slightly higher viscosity result (2125 cps) was found compared to the results obtained for the other batches (2043 cps, 2073 cps, 2075 cps) stored at that condition. Correspondingly slightly elevated assay results for clozapine and preservatives at those stations are evidence that moisture has been lost from the product. It was suspected that the caps on the individual bottles were not fully secured. For the 1000 L commercial batches a new machine part has been used to secure the closures and no change in viscosity has been observed.

pH

The pH results of the four batches of Clozapine Suspension (upright and inverted) remained constant and well within the specifications when stored at 25 °C/60 % RH. A slight decrease in the pH was observed for all batches when stored at 40 °C/75 % RH for six months, however, the results remained within specification.

Related Substances

No individual impurities over 0.1 % were found in any of the batches of Clozapine Suspension (upright and inverted) when stored at 25 °C/60 % RH for up to 24-months. It can be observed that the number of individual unknown impurities detected is increasing over time, though most of them are seen below the Limit of Quantification only.

The level of Impurity A increased over time up to a level of 0.12 % after storage for 6 months at 40 °C/75 % RH, but is still well within the specified limit of not more than 0.2 %.

There is an increasing trend for total impurities however the results are below the specification limit for all batches of Clozapine Suspension at the stability conditions tested.

Assay - Clozapine

For the registration batches an out-of-specification assay result was observed for batch 17298 (111 %), after six months storage at 40 °C/75 % RH. When compared to batches 17359 (101 %), 17361 (inverted; 100 %) and 17361 (upright; 103 %) stored at this condition the result appears uncharacteristic. At 18-months, batch 17298 stored at 25 °C/60 % RH also had an assay result just out of specification (106 %). Correspondingly slightly higher results were also obtained for viscosity (6 months 40 °C/75 % RH and 18 months 25 °C/60 % RH) and assay of propyl paraben sodium (6 months 40°C/75 % RH). This suggests that the increase in assay is most likely due to the closure on those bottles not being adequately secured, leading to evaporation of moisture from the product. Similarly, it was also noted that batch 17361 (upright), when stored for 12 months at 25 °C/60 % RH had a slightly higher assay (105 %) than that of batches 17298 (103 %), 17361 (inverted; 102 %) and 17359 (102 %) at the same stability station. This slightly higher clozapine assay suggests some moisture loss from some of the unit containers on storage as well.

The problem with the secure fitting of the cap onto the bottles was identified on the registration batches and has since been rectified with new tooling fitted on the capping machine. A further two batches of Clozapine Suspension (Batch 23283 and 32126) have been manufactured and packed using the new tooling. The assay results obtained so far up to 24 and 12-months are satisfactory with all results within specification.

The assay result for Clozapine at time zero for batch 17361 was low at 96 %, compared to batches 17298 and 17359 that were manufactured at the same time, these being 101 % and 99 % respectively. At the time, the low result obtained for batch 17361 was not considered significant since it was within specification. However, during the stability study it was noted that the assay result was seen to be higher at about 103 % which remained fairly consistent from three months onwards, ranging from 100 to 105 % (samples stored upright at 25°C / 60 % RH). Also, the assay results of batch 17361 stored inverted at 25°C / 60 % RH, show similar behaviour with most results within a relatively consistent range of 99 to 103 %. Subsequent review of the process evaluation data obtained for batch 17361 on packed product taken throughout the bottling procedure revealed consistent clozapine assay results of 101 to 104 % as well. In retrospect, taking the above into consideration, the low result of 96 % was not representative.

Some variation in assay results was noticed for all batches although no obvious trends were discernable. Some of the differences observed are most probably caused by incomplete mixing of the suspension at the time of assay. It has since been determined that when the suspension has been stored for long periods, extra mixing time is required to ensure homogeneity of the suspension. The mixing instruction of the analytical method was revised at the 18 months stability time-point for the first three registration batches (17298, 17359, 17361) and now states that the suspension is to be thoroughly mixed ensuring no clozapine is observed on the bottom of the bottle.

Whilst the accuracy and reproducibility of the analytical method for assay has been shown, it is clear that there is some variability observed, generally ranging between 99 and 103 %. No obvious trends are seen in the batches, nor are any other parameters affected by the slight fluctuations in assay. The variability of results is consistent between batches and has been seen on stability, as well as during validation of the assay method and other investigational work.

Taking the above factors into consideration, the variability of the assay results on stability can be accepted as overall the assay for Clozapine remained within specification after 24 months storage at 25 °C/60 % RH and six months at 40 °C/75 % RH with no obvious trends observed. Additionally, all other parameters tested remain within specification.

Assay - Methyl paraben sodium

The assay of the methyl paraben sodium in the four batches of Clozapine Suspension (upright and inverted) showed a trend to decrease over the storage period at 25 °C/60 % RH. It was noted that a more rapid decrease for all batches (upright and inverted) was observed after six months storage at 40 °C/75 % RH.

For batch 23283 (inverted) after storage at 40 °C/75 % RH for six months a low result just out of specification (69 %) was found. However preservative efficacy testing was performed at this time-point and the result complied, showing sufficient preservative properties. Therefore the low result can be accepted as an exception. All other results were within the shelf life specification.

It was also noted that for registration batch 17298, a higher assay result (80 %) after storage at 40 °C/75 % RH for six months was obtained when compared to batches 17359 (74 %), 17361 (inverted; 76 %) and 17361 (upright; 75 %) when stored at the same stability conditions. Correspondingly higher results were also obtained for viscosity and assay of clozapine indicating that the closure on this particular bottle had not been adequately secured, leading to evaporation of moisture from the product.

Assay – Propyl paraben sodium

The assay of the propyl paraben sodium showed an overall trend to decrease at 25 °C/60 % RH and 40 °C/75 % RH with results remaining within the shelf life specifications at 25 °C/60 % RH.

It was noted that for batch 17298 a higher assay result (102 %) after storage at 40 °C/75 % RH for six months was obtained when compared to batches 17359 (94 %), 17361 (inverted; 91 %) and 17361 (upright; 93 %) when stored at the same stability conditions. Correspondingly higher results were also obtained for viscosity and assay of clozapine indicating that the closure on this particular bottle had not been adequately secured leading to evaporation of moisture from the product.

Microbial Limits

The microbial results for all batches of Clozapine Suspension (upright and inverted) remained constant over the six month storage at 40 °C/75 % RH. The results are well within the specification. Microbial limits were also tested for batches 17298, 17359 and 17361 at 24-months at 25 °C/60 % RH and found to be well within specification.

2) Photo-stability

Stability Protocol

A photostability study has been conducted to ascertain if the packaging for Clozapine 50 mg/ml Suspension provides adequate protection for the product when exposed to light as per the ICH guidelines Q1B Stability Testing: Photo-stability testing of new drug substances and products (CPMP/ICH/279/95).

Clozapine Suspension was exposed to light in accordance to ICH guidelines on photo-stability (CPMP/ICH/279/95) using light source option two (cool white fluorescent lamp and a near UV fluorescent lamp) for not less than 200 watt hours/ m^2 and 1.2 million lux hours.

Study Design

The following control and samples were used in the photo-stability study.

Control - Clozapine 50 mg/ml Suspension (ie. amber glass bottles fitted with TE/CR PP Caps) that was not subjected to any photo-stressing.

Sample 1 - Suspension outside of the immediate pack.
Suspension from two bottles of Clozapine 50 mg/ml Suspension was removed from the protective bottles and placed into separate glass beakers. The suspension was then exposed as per the ICH photo-stability conditions.

Sample 2 - Suspension in the immediate (primary) pack.
Two bottles of Clozapine 50 mg/ml Suspension (ie. amber glass bottles fitted with TE/CR PP Caps) were exposed as per the ICH photo-stability conditions.

Sample 3 - Suspension in the marketing pack.
Two bottles of Clozapine 50 mg/ml Suspension (ie. amber glass bottles fitted with TE/CR PP Caps) enclosed inside cardboard boxes were exposed as per the ICH photo-stability conditions.

Characteristics studied

Clozapine Suspension was tested according to the shelf life specifications and the tests include:

Physical Characteristics

- Description
- Viscosity

Chemical characteristics

- pH
- Related Substances
- Assay:
  - Clozapine
  - Methyl paraben sodium
  - Propyl paraben sodium

Limits for these tests are located in the Shelf Life Specifications, presented in Appendix 1. Samples were analysed according to the current analytical procedures at the time of testing.

Summary of results

Tabular results from the photostability study are provided in Appendix 2.

Description
For all presentations studied, the appearance of the suspension is consistent indicating that the suspension is unaffected by photo-stressing.

Viscosity
The viscosity of the suspension was unaffected by photo-stressing for all presentations studied.

Specific gravity
For all presentations, the specific gravity of the suspension was unaffected by photo-stressing. All results were within the acceptance limits.

pH
For all presentations studied, the pH of the suspension is identical showing that the suspension is unaffected by photo-stressing.

Assay - Clozapine
The assay of clozapine was unaffected by photo-stressing when stored in the immediate and marketing pack. Where the suspension was stored outside the immediate packaging (sample 1) the assay result was slightly out of specification (107 %). The increase seen was due to evaporation of the sample rather than any photo effects as supported by the low related substances observed for sample 1 which was similar to those of suspension in the immediate (primary) pack (sample 2) and suspension in the marketing pack (sample 3).

Assay - Methyl paraben sodium
For all presentations studied, the assay of methyl paraben sodium was unaffected by photo-stressing. Where the suspension was stored outside the immediate packaging (sample 1) the assay increased slightly however the result is still within specification.

Assay - Propyl paraben sodium
The assay of propyl paraben sodium was unaffected by photo-stressing when the suspension was packed in the immediate and marketing pack. Where the suspension was stored outside the immediate packaging (sample 1) the assay increased slightly however the result is still within specification.

Related substances
The related substances of clozapine for all presentations remained well below the acceptance limits and was unaffected by photo-stressing.

Overall Stability Conclusion

Stability results obtained show acceptable stability up to 24 months at 25 °C/60 % RH and 6 months 40 °C/75 % RH for all batches.

The results obtained for photostability showed that the immediate (primary) packaging (amber glass bottles and CR/TE white PP caps) is sufficient to protect the product from the photo-stability conditions prescribed by the ICH guidance. This indicates that the appropriate packaging for the product has been chosen with respect to light protection.

The following shelf life and label storage conditions are proposed based on stability data generated to date.

Product	Shelf-life	Label Storage Conditions
Clozapine 50 mg/ml Suspension	24 months	Store in original container

Product: Clozapine Suspension 50 mg/ml
Batch No. 17298 (Bulk: 17285)
Active Batch No(s). : A6482
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle with PP CRC/TE cap

Date of manufacture: December 04
Start of stability: January 05
Storage conditions: 25°C / 60% RH

Test		Months 0	3	6	9	12	18	24	36	48	60
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	*	+	+
Viscosity (cps)		2162	2083	2077	2188	2083	2125	2068	+	+	+
pH		6.8	6.7	6.7	6.7	6.7	6.7	6.6	+	+	+
Related Substances (%)											
	Impurity A	<0.01	0.02	0.02	0.03	0.04	0.06	0.08	+	+	+
	Impurity B	0.02	0.02	0.02	0.02	0.02	0.02	0.02	+	+	+
	Impurity C	ND	0.02	0.03	0.02	0.02	0.02	0.01	+	+	+
	Unspecified Impurities (individual)	0.01, <0.01 <0.01, <0.01	0.02, <0.01, 0.05, <0.01	0.02, 0.01, <0.01, <0.01	0.02, <0.01 0.01	0.02, <0.01, 0.01, 0.01	0.01, <0.01, <0.01, <0.01, <0.01	0.03, <0.01, <0.01, <0.01, <0.01	+	+	+
	Total Impurities (%)	0.03	0.13	0.10	0.10	0.12	0.11	0.14	+	+	+
Assay (HPLC)											
Clozapine	mg/mL	50.5	50.4	50.6	52.2	51.7	52.9	52.5	+	+	+
	% of the labelled content	101	101	101	104	103	106	105	+	+	+
Sodium methyl parahydroxybenzoate (mg/mL)		1.93	1.92	1.88	1.79	1.76	1.67	1.62	+	+	+
Sodium propyl parahydroxybenzoate (mg/mL)		0.198	0.200	0.202	0.197	0.196	0.190	0.190	+	+	+
Microbiological Tests (CFU/g)											
	Total Viable Aerobic Count	<10/g	NT	NT	NT	NT	NT	<10/g	+	+	+
	Fungi (Yeasts and Moulds)	<10/g	NT	NT	NT	NT	NT	<10/g	+	+	+
	Escherichia coli	ND /g	NT	NT	NT	NT	NT	ND /g	+	+	+

NT = Not Tested NMT = Not More Than ND=Not Detected

Product: Clozapine Suspension 50 mg/ml
Batch No. 17298 (Bulk: 17285)
Active Batch No(s). : A6482
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle with PP CRC/TE cap

Date of manufacture: December 04
Start of stability: January 05
Storage conditions: 40°C / 75% RH

		Months		
Test		0	3	6
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.
Viscosity (cps)		2162	2125	2536
pH		6.8	6.6	6.6
Related Substances (%)				
	Impurity A	<0.01	0.06	0.12
	Impurity B	0.02	0.02	0.02
	Impurity C	ND	0.03	0.02
	Unspecified Impurities (individual)	0.01, <0.01, <0.01, <0.01	<0.01, <0.01, 0.05, <0.01	0.01, 0.01, <0.01, <0.01
	Total Impurities (%)	0.03	0.16	0.18
Assay (HPLC)				
Clozapine	mg/mL	50.5	50.6	55.7
	% of the labelled content	101	101	111
Sodium methyl parahydroxybenzoate (mg/mL)		1.93	1.68	1.60
Sodium propyl parahydroxybenzoate (mg/mL)		0.198	0.195	0.204
Microbiological Tests (CFU/g)				
	Total Viable Aerobic Count	<10/g	NT	<10/g
	Fungi (Yeasts and Moulds)	<10/g	NT	<10/g
	Escherichia coli	None detected /g	NT	None detected /g

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50 mg/ml
Batch No. 17359 (Bulk: 17346)
Active Batch No(s). : A6482
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle with PP CRC/TE cap

Date of manufacture: December 04
Start of stability: January 05
Storage conditions: 25°C / 60% RH

		Months									
Test		0	3	6	9	12	18	24	36	48	60
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	+	+	+
Viscosity		2173	2045	2038	2030	2057	2043	2003	+	+	+
pH		6.8	6.8	6.8	6.7	6.7	6.7	6.6	+	+	+
Related Substances											
	Impurity A	<0.01	0.01	0.02	0.03	0.04	0.06	0.08	+	+	+
	Impurity B	0.02	0.02	0.01	0.02	0.01	0.02	0.02	+	+	+
	Impurity C	ND	0.02	0.02	0.02	0.02	0.02	0.02	+	+	+
	Unspecified Impurities (individual)	<0.01	0.02, <0.01, 0.05, <0.01	0.02, <0.01, <0.01, <0.01	0.03,<0.01, 0.01	0.02, <0.01, 0.01, 0.01	0.01, <0.01, <0.01, <0.01, <0.01	0.03, <0.01, <0.01, <0.01, <0.01	+	+	+
	Total Impurities (%)	0.02	0.12	0.07	0.11	0.11	0.11	0.15	+	+	+
Assay (HPLC)											
Clozapine	mg/mL	49.6	50.2	51.5	50.1	51.3	50.4	50.2	+	+	+
	% of the labelled content	99	100	103	100	103	101	100	+	+	+
Sodium methyl parahydroxybenzoate (mg/mL)		1.98	1.90	1.86	1.78	1.76	1.65	1.60	+	+	+
Sodium propyl parahydroxybenzoate (mg/mL)		0.202	0.203	0.200	0.194	0.199	0.186	0.187	+	+	+
Microbiological Tests											
	Total Viable Aerobic Count	<10/g	NT	NT	NT	NT	NT	<10/g	+	+	+
	Fungi (Yeasts and Moulds)	<10/g	NT	NT	NT	NT	NT	<10/g	+	+	+
	Escherichia coli	ND/g	NT	NT	NT	NT	NT	ND/g	+	+	+

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50 mg/ml
Batch No. 17359 (Bulk: 17346)
Active Batch No(s). : A6482
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle with PP CRC/TE cap

Date of manufacture: December 04
Start of stability: January 05
Storage conditions: 40°C / 75% RH

		Months		
Test		0	3	6
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.
Viscosity		2173	2083	2043
pH		6.8	6.6	6.6
Related Substances				
	Impurity A	<0.01	0.05	0.11
	Impurity B	0.02	0.02	0.02
	Impurity C	ND	0.03	0.02
	Unspecified Impurities (individual)	<0.01	0.01, <0.01 0.05, <0.01	<0.01, 0.01 0.01, 0.01 <0.01, <0.01
	Total Impurities (%)	0.02	0.16	0.18
Assay (HPLC)				
Clozapine	mg/mL	49.6	51.9	50.4
	% of the labelled content	99	104	101
Sodium methyl parahydroxybenzoate (mg/mL)		1.98	1.64	1.47
Sodium propyl parahydroxybenzoate (mg/mL)		0.202	0.195	0.188
Microbiological Tests				
	Total Viable Aerobic Count	<10/g	NT	<10/g
	Fungi (Yeasts and Moulds)	<10/g	NT	<10/g
	Escherichia coli	ND/g	NT	ND/g

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50mg/ml
Batch No. 17361 (Bulk: 17347)
Active Batch No(s). : A6482
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle with PP CRC/TE cap

Date of manufacture: December 04
Start of stability: January 05
Storage conditions: 25°C / 60% RH

		Months									
Test		0	3	6	9	12	18	24	36	48	60
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	+	+	+
Viscosity (cps)		2192	2070	2055	2068	2063	2085	2073	+	+	+
pH		6.8	6.8	6.7	6.7	6.7	6.6	6.6	+	+	+
Related Substances (%)											
	Impurity A	<0.01	0.02	0.02	0.03	0.04	0.06	0.08	+	+	+
	Impurity B	0.01	0.02	0.02	0.01	0.02	0.02	0.02	+	+	+
	Impurity C	ND	0.03	0.02	0.02	0.02	0.02	0.01	+	+	+
	Unspecified Impurities (individual)	<0.01, <0.01	0.02, <0.01, 0.06, <0.01	0.02, 0.01, <0.01, <0.01, <0.01	0.03, <0.01, <0.01, 0.01	0.02, 0.01, 0.01, 0.01	0.01, <0.01, <0.01, <0.01, <0.01	0.03, <0.01, <0.01, <0.01, <0.01, <0.01	+	+	+
	Total Impurities (%)	0.01	0.15	0.09	0.10	0.13	0.11	0.14	+	+	+
Assay (HPLC)											
Clozapine	mg/mL	47.8	50.0	51.3	51.3	52.7	51.4	51.4	+	+	+
	% of the labelled content	96	100	103	103	105	103	103	+	+	+
Sodium methyl parahydroxybenzoate (mg/mL)		1.98	1.90	1.87	1.82	1.75	1.66	1.62	+	+	+
Sodium propyl parahydroxybenzoate (mg/mL)		0.201	0.199	0.198	0.197	0.194	0.187	0.188	+	+	+
Microbiological Tests (CFU/g)											
	Total Viable Aerobic Count	<10/g	NT	NT	NT	NT	NT	<10/g	+	+	+
	Fungi (Yeasts and Moulds)	<10/g	NT	NT	NT	NT	NT	<10/g	+	+	+
	Escherichia coli	ND /g	NT	NT	NT	NT	NT	ND /g	+	+	+

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50mg/ml
Batch No. 17361 (Bulk: 17347)
Active Batch No(s). : A6482
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle with PP CRC/TE cap

Date of manufacture: December 04
Start of stability: January 05
Storage conditions: 40°C / 75% RH

Test		Months 0	3	6
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.
Viscosity (cps)		2192	2122	2122
pH		6.8	6.6	6.6
Related Substances (%)				
	Impurity A	<0.01	0.05	0.11
	Impurity B	0.01	0.02	0.02
	Impurity C	ND	0.03	0.02
	Unspecified Impurities (individual)	<0.01, <0.01	0.01, <0.01, 0.06, <0.01	<0.01, 0.01, 0.01, 0.01, <0.01, <0.01
	Total Impurities (%)	0.01	0.17	0.18
Assay (HPLC)				
Clozapine	mg/mL	47.8	51.1	51.3
	% of the labelled content	96	102	103
Sodium methyl parahydroxybenzoate (mg/mL)		1.98	1.65	1.49
Sodium propyl parahydroxybenzoate (mg/mL)		0.201	0.190	0.186
Microbiological Tests (CFU/g)				
	Total Viable Aerobic Count	<10/g	NT	<10/g
	Fungi (Yeasts and Moulds)	<10/g	NT	<10/g
	Escherichia coli	ND /g	NT	ND /g

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50mg/ml
Batch No. 17361 Inverted (Bulk: 17347)
Active Batch No(s). : A6482
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle with PP CRC/TE cap

Date of manufacture: December 04
Start of stability: January 05
Storage conditions: 25°C / 60% RH

Test		Months 0	3	6	9	12	18	24	36	48	60
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	+	+	+
Viscosity (cps)		2192	2110	2095	2062	2075	2082	2075	+	+	+
pH		6.8	6.8	6.7	6.8	6.7	6.7	6.6	+	+	+
Related Substances (%)											
	Impurity A	<0.01	0.01	0.02	0.03	0.04	0.06	0.09	+	+	+
	Impurity B	0.01	0.02	0.02	0.02	0.02	0.02	0.02	+	+	+
	Impurity C	ND	0.02	0.02	0.02	0.02	0.02	0.02	+	+	+
	Unspecified Impurities (individual)	<0.01, <0.01	0.02, <0.01, 0.06, <0.01	0.02, 0.01, 0.01, <0.01, <0.01	0.03, <0.01, 0.01	0.02, <0.01, 0.01, 0.01	0.01, <0.01, <0.01, <0.01, <0.01	0.03, <0.01, <0.01, <0.01, <0.01	+	+	+
	Total Impurities (%)	0.01	0.13	0.10	0.11	0.12	0.11	0.16	+	+	+
Assay (HPLC)											
Clozapine	mg/mL	47.8	51.0	49.6	49.8	51.2	51.3	48.5	+	+	+
	% of the labeled content	96	102	99	100	102	103	97	+	+	+
Sodium methyl parahydroxybenzoate (mg/mL)		1.98	1.92	1.86	1.80	1.75	1.66	1.62	+	+	+
Sodium propyl parahydroxybenzoate (mg/mL)		0.201	0.198	0.198	0.192	0.199	0.186	0.187	+	+	+
Microbiological Tests (CFU/g)											
	Total Viable Aerobic Count	<10/g	NT	NT	NT	NT	NT	<10/g	+	+	+
	Fungi (Yeasts and Moulds)	<10/g	NT	NT	NT	NT	NT	<10/g	+	+	+
	Escherichia coli	ND /g	NT	NT	NT	NT	NT	ND /g	+	+	+

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50mg/ml
Batch No. 17361 Inverted (Bulk: 17347)
Active Batch No(s). : A6482
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle with PP CRC/TE cap

Date of manufacture: December 04
Start of stability: January 05
Storage conditions: 40°C / 75% RH

		Months		
Test		0	3	6
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.
Viscosity (cps)		2192	2072	2098
pH		6.8	6.8	6.6
Related Substances (%)				
	Impurity A	<0.01	0.05	0.11
	Impurity B	0.01	0.02	0.02
	Impurity C	ND	0.03	0.03
	Unspecified Impurities (individual)	<0.01, <0.01	0.01, <0.01, 0.05, <0.01	<0.01, 0.01, <0.01, 0.01, <0.01, <0.01
	Total Impurities (%)	0.01	0.16	0.18
Assay (HPLC)				
Clozapine	mg/mL	47.8	50.9	50.1
	% of the labelled content	96	102	100
Sodium methyl parahydroxybenzoate (mg/mL)		1.98	1.67	1.46
Sodium propyl parahydroxybenzoate (mg/mL)		0.201	0.191	0.182
Microbiological Tests (CFU/g)				
	Total Viable Aerobic Count	<10/g	NT	<10/g
	Fungi (Yeasts and Moulds)	<10/g	NT	<10/g
	Escherichia coli	ND /g	NT	ND /g

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50mg/ml
Batch No. 23283 (Bulk: 23104)
Active Batch No(s). : A21881
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle (125ml) with PP CRC/TE cap

Date of manufacture: 03/04/07
Start of stability: 08/06/07
Storage conditions: 25°C / 60% RH
Specification: SLS CLOZ SUSP

		Months							
Test		0	3	6	9	12	18	24	36
Description		A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter
Viscosity (cps)		2297	2273	2267	2233	2245	2418	2243	2197
Specific Gravity		1.07	1.08	1.08	1.07	1.08	1.08	1.08	1.08
pH		6.8	6.7	6.7	6.7	6.7	6.7	6.7	6.8
Related Substances (%)									
	Impurity A	<0.01	0.02	0.02	0.04	0.05	0.08	0.09	0.12
	Impurity B	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
	Impurity C	0.04	0.03	0.04	0.04	0.04	0.03	0.03	0.04
	Unspecified Impurities (individual)	0.02, <0.01, <0.01 <0.01	0.03, <0.01, <0.01, <0.01,	0.02, <0.01, <0.01 <0.01, <0.01, <0.01, <0.01, <0.01	<0.01, 0.02, <0.01,	0.02, <0.01, <0.01	0.02, <0.01, 0.03, <0.01	0.03, <0.01, <0.01, <0.01, <0.01, <0.01	0.03, <0.01, <0.01, 0.01, <0.01, 0.03, <0.01,
	Total Impurities (%)	0.09(3)	0.11(4)	0.11 (4)	0.13(4)	0.14(5)	0.16(4)	0.18(4)	0.26(6)
Assay (HPLC)									
Clozapine	mg/ml	50.2	49.2	51.0	49.8	51.6	51.4	50.5	49.9
	% of the labelled content	100.4	98.4	102	99.8	103.2	102.7	101	99.8
Sodium methyl parahydroxybenzoate (mg/ml)		1.93	1.85	1.85	1.74	1.76	1.65	1.62	1.49
Sodium propyl parahydroxybenzoate (mg/ml)		0.203	0.201	0.200	0.198	0.196	0.201	0.198	0.192
Uniformity of Dosage Units		NT	NT	NT	NT	Complies	Complies	Complies	Complies
Microbiological Tests									
	Total Aerobic Microbial Count	<10/g	NT	NT	NT	NT	NT	<10/g	<10/g
	Fungi (Yeasts and Moulds)	<10/g	NT	NT	NT	NT	NT	<10/g	<10/g
	Enterbacteriaceae	<10/g	NT	NT	NT	NT	NT	NT	NT
	E. Coli	ND /g	NT	NT	NT	NT	NT	Absent/g	Absent/g
	Salmonella	ND/10g	NT	NT	NT	NT	NT	NT	NT
Weight Loss (%)		NT	0.01	0.01	0.01	0.02	0.02	0.03	0.04

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50 mg/ml
Batch No. 23283 (Bulk: 23104)
Active Batch No(s). : A21881
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle (125ml) with PP CRC/TE cap

Date of manufacture: 03/04/07
Start of stability: 08/06/07
Storage conditions: 40°C / 75% RH
Specification: SLS CLOZ SUSP

		Months		
Test		0	3	6
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.
Viscosity (cps)		2297	2262	2250
Specific Gravity		1.07	1.08	1.08
pH		6.8	6.6	6.5
Related Substances (%)				
	Impurity A	<0.01	0.06	0.12
	Impurity B	0.03	0.03	0.03
	Impurity C	0.04	0.03	0.04
	Unspecified Impurities (individual)	0.02,<0.01, <0.01,<0.01	0.02,<0.01, <0.01 ,<0.01	0.01, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01
	Total Impurities (%)	0.09(3)	0.14(4)	0.20 (4)
Assay (HPLC)				
Clozapine	mg/ml	50.2	50.4	50.1
	% of the labelled content	100.4	100.8	100.2
Sodium methyl parahydroxybenzoate (mg/ml)		1.93	1.60	1.45
Sodium propyl parahydroxybenzoate (mg/ml)		0.203	0.192	0.188
Uniformity of Dosage Units		NT	NT	Complies
Microbiological Tests				
	Total Aerobic Microbial Count	<10/g	<10/g	<10/g
	Fungi (Yeasts and Moulds)	<10/g	<10/g	<10/g
	Enterbacteriaceae	<10/g	<10/g	<10/g
	E. Coli	None detected /g	None detected /g	None detected /g
	Salmonella	None detected /10g	None detected /10g	None detected /10g
Weight Loss (%)		NT	0.00	0.01

NT = Not teste NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50 mg/ml (Inverted)
Batch No. 23283 (Bulk: 23104)
Active Batch No(s). : A21881
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle (125ml) with PP CRC/TE cap

Date of manufacture: 03/04/07
Start of stability: 08/06/07
Storage conditions: 25°C / 60% RH
Specification: SLS CLOZ SUSP

		Months							
Test		0	3	6	9	12	18	24	36
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	+
Viscosity (cps)		2297	2277	2278	2222	2243	2522	2252	+
Specific Gravity		1.07	1.08	1.08	1.07	1.07	1.08	1.08	+
pH		6.8	6.7	6.7	6.7	6.7	6.6	6.6	+
Related Substances (%)									
	Impurity A	<0.01	0.02	0.02	0.04	0.05	0.08	0.09	+
	Impurity B	0.03	0.03	0.03	0.03	0.03	0.03	0.03	+
	Impurity C	0.04	0.03	0.04	0.04	0.04	<0.01	0.03	+
	Unspecified Impurities (individual)	0.02,<0.01, <0.01 ,<0.01	0.03,<0.01, <0.01, <0.01,	0.02,<0.01, <0.01,<0.01, <0.01, <0.01, <0.01, <0.01	<0.01, 0.02, <0.01	0.02, <0.01, <0.01	0.02, <0.01, 0.03	0.03, <0.01, <0.01, <0.01, <0.01, <0.01,	+
	Total Impurities (%)	0.09(3)	0.11(4)	0.11 (4)	0.13(4)	0.15(4)	0.16(4)	0.19(4)	+
Assay (HPLC)									
Clozapine	mg/ml	50.2	49.6	48.6	49.5	49.9	51.3	50.4	+
	% of the labelled content	100.4	99.2	97.2	99	99.7	102.5	100.8	+
Sodium methyl parahydroxybenzoate (mg/ml)		1.93	1.85	1.84	1.76	1.75	1.67	1.52	+
Sodium propyl parahydroxybenzoate (mg/ml)		0.203	0.203	0.199	0.200	0.194	0.203	0.199	+
Uniformity of Dosage Units		NT	NT	NT	NT	NT	Complies	Complies	+
Microbiological Tests									
	Total Aerobic Microbial Count	<10/g	NT	NT	NT	NT	NT	<10/g	+
	Fungi (Yeasts and Moulds)	<10/g	NT	NT	NT	NT	NT	<10/g	+
	Enterbacteriacese	<10/g	NT	NT	NT	NT	NT	NT	+
	E. Coli	None detected /g	NT	NT	NT	NT	NT	absent/g	+
	Salmonella	None detected /10g	NT	NT	0.01	NT	NT	NT	+
Weight Loss (%)		NT	0.00	0.00	0.01	0.01	0.01	0.01	+

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50 mg/ml (Inverted)
Batch No. 23283 (Bulk: 23104)
Active Batch No(s). : A21881
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle (125ml) with PP CRC/TE cap

Date of manufacture: 03/04/07
Start of stability: 08/06/07
Storage conditions: 40°C / 75% RH
Specification: SLS CLOZ SUSP

Test		Months 0	3	6
Description		A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.	A free flowing suspension, free from particulates and foreign matter.
Viscosity (cps)		2297	2265	2235
Specific Gravity		1.07	1.08	1.08
pH		6.8	6.6	6.5
Related Substances (%)				
	Impurity A	<0.01	0.07	0.12
	Impurity B	0.03	0.03	0.02
	Impurity C	0.04	0.03	0.04
	Unspecified Impurities (individual)	0.02,<0.01, <0.01 ,<0.01	0.02,<0.01, 0.01 ,<0.01	<0.01,<0.01 <0.01, <0.01 <0.01, <0.01,
	Total Impurities (%)	0.09(3)	0.16(5)	0.18 (3)
Assay (HPLC)				
Clozapine	mg/ml	50.2	48.9	48.9
	% of the labelled content	100.4	97.8	97.8
Sodium methyl parahydroxybenzoate (mg/ml)		1.93	1.62	1.37
Sodium propyl parahydroxybenzoate (mg/ml)		0.203	0.195	0.186
Uniformity of Dosage Units		NT	NT	Complies
Microbiological Tests				
	Total Aerobic Microbial Count	<10/g	<10/g	<10/g
	Fungi (Yeasts and Moulds)	<10/g	<10/g	<10/g
	Enterbacteriaceae	<10/g	<10/g	<10/g
	E. Coli	None detected /g	None detected /g	None detected /g
	Salmonella	None detected /10g	None detected /10g	None detected /10g
Weight Loss (%)		NT	0.00	0.01

NT = Not teste NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50mg/ml
Batch No. 32126(Bulk: 31834)
Active Batch No(s). : 31586
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle (125ml) (300942)with PP CRC/TE cap(300941)

Date of manufacture: Oct.2008
Start of stability: 19/12/2008
Storage conditions: 25°C / 60% RH
Specification: SLS CLOZ SUSP Cat 0

Test		Months 0	3	6	9	12	18	24	36
Description		A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	A free flowing yellow suspension, free from particulates and foreign matter	+	+	+
Viscosity (cps)		2287	2252	2300	2170	2127	+	+	+
Specific Gravity		1.09	1.08	1.08	1.08	1.08	+	+	+
pH		6.8	6.8	6.8	6.8	6.7	+	+	+
Related Substances (%)									
	Impurity A	<0.01	0.02	0.03	0.04	0.05	+	+	+
	Impurity B	0.02	0.02	0.02	0.02	0.02	+	+	+
	Impurity C	ND	0.01	<0.01	<0.01	0.01	+	+	+
	Unspecified Impurities (individual)	0.03, 0.03, 0.02, <0.01, <0.01, <0.01	0.03, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01	0.04, < 0.01, <0.01, <0.01, <0.01, <0.01	0.04, <0.01, <0.01, <0.01	0.04, <0.01, 0.01, 0.01, <0.01, 0.03, <0.01, <0.01	+	+	+
	Total Impurities (%)	0.09(4)	0.09(4)	0.09(3)	0.10(3)	0.17(7)	+	+	+
Assay (HPLC)									
Clozapine	mg/ml	49.8	50	49.7	50.1	49.5	+	+	+
	% of the labelled content	100	100	99	100	99	+	+	+
Sodium methyl parahydroxybenzoate (mg/ml)		2.01	1.93	1.82	1.8	1.73	+	+	+
Sodium propyl parahydroxybenzoate (mg/ml)		0.193	0.195	0.182	0.191	0.189	+	+	+
Uniformity of Dosage Units		Complies	NT	NT	NT	NT	+	+	+
Microbiological Tests									
	Total Aerobic Microbial Count	<10/g	NT	NT	NT	NT	+	+	+
	Fungi (Yeasts and Moulds)	<10/g	NT	NT	NT	NT	+	+	+
	Enterbacteriacese	<10/g	NT	NT	NT	NT	+	+	+
	E. Coli	ND/g	NT	NT	NT	NT	+	+	+
	Salmonella	ND/10g	NT	NT	NT	NT	+	+	+
Weight Loss (%)		N/A	0	0	0	0	+	+	+

NT = Not tested NMT = Not more than ND=Not Detected

Product: Clozapine Suspension 50mg/ml
Batch No. 32126(Bulk: 31834)
Active Batch No(s). : 31586
Composition: Formulation as applied for

Active manufacturer: Medichem
Dosage form manufacturer: Douglas
Packaging: Amber Glass Bottle (125ml) (300942)with PP CRC/TE cap(300941)

Date of manufacture: Oct.2008
Start of stability: 19/12/2008
Storage conditions: 40°C / 75% RH
Specification: SLS CLOZ SUSP

Test		Months 0	3	6
Description		A free flowing yellow suspension, free from particulates and foreign matter.	A free flowing yellow suspension, free from particulates and foreign matter.	A free flowing yellow suspension, free from particulates and foreign matter
Viscosity (cps)		2287	2185	2346
Specific Gravity		1.09	1.08	1.08
pH		6.8	6.8	6.8
Related Substances (%)				
	Impurity A	<0.01	0.06	0.11
	Impurity B	0.02	0.01	0.02
	Impurity C	ND	0.01	<0.01
	Unspecified Impurities (individual)	0.03, 0.03, 0.02, <0.01, <0.01, <0.01	0.03, <0.01, <0.01, <0.01, <0.01, <0.01	0.05, <0.01, <0.01, <0.01, <0.01, <0.01, <0.01
	Total Impurities (%)	0.09(4)	0.12(4)	0.18(3)
Assay (HPLC)				
Clozapine	mg/ml	49.8	50.9	50.4
	% of the labelled content	100	102	100
Sodium methyl parahydroxybenzoate (mg/ml)		2.01	1.73	1.43
Sodium propyl parahydroxybenzoate (mg/ml)		0.193	0.19	0.177
Uniformity of Dosage Units		#REF!	NT	NT
Microbiological Tests				
	Total Aerobic Microbial Count	ND/10g	NT	<10/g
	Fungi (Yeasts and Moulds)	N/A	NT	<10/g
	Enterbacteriaceae	Complies	NT	Absent/g
	E. Coli	#REF!	NT	NT
	Salmonella	#REF!	NT	NT
Weight Loss (%)		#REF!	0.00	0

NT = Not teste NMT = Not more than ND=Not Detected

Exhibit B

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1438/001/005
Case No: 2049687

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Merz Pharma UK Ltd

260 Centennial Park, Elstree Hill South, Elstree, Hertfordshire WD6 3SR, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Denzapine 50mg/ml Oral Suspension

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **06/03/2009 until 05/03/2014.**

Signed on behalf of the Irish Medicines Board this 6th March 2009

Sabrina J. Mulligan.

A person authorised in that behalf by the said Board.

Bord Leigheasra na hÉireann
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: 353-1-676 4971 Fax: 353-1-676 7836
Website: www.imb.ie

Part I

Product Specific Details

1 PRODUCT AUTHORISATION NUMBER

PA1438/1/5

2 NAME OF THE MEDICINAL PRODUCT

Denzapine 50mg/ml Oral Suspension

DENZAPINE can cause agranulocytosis. Its use should be limited to patients:

- **with schizophrenia who are non-responsive to or intolerant of antipsychotic drug treatment, or with psychosis in Parkinson's disease when other treatment strategies have failed (see point 4.1)**
- **who have initially normal leukocyte findings (white blood cell count of >3500/mm^3 (3.5 x 10^9 /L), and an absolute neutrophil count (ANC) of >2000/mm^3 (2.0 x 10^9 /L)), and**
- **in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of DENZAPINE**

Prescribing physicians should comply with the required safety measures. At each consultation, a patient receiving DENZAPINE should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

DENZAPINE must be dispensed under strict medical supervision in accordance with official recommendations.

Myocarditis

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely.

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction.

If myocarditis or cardiomyopathy are suspected, DENZAPINE treatment should be promptly stopped and the patient immediately referred to a cardiologist.
Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

3 PRODUCT DESCRIPTION

Oral suspension

Free-flowing yellow suspension

4 COMPOSITION

	Quantity
Active Substance	
Clozapine Ph.Eur.	50.00 mg/ml
Excipient(s)	
Sorbitol Liquid (crystallising) Ph.Eur.	150.00 mg/ml
Povidone K90 Ph.Eur.	10.00 mg/ml
Sodium dihydrogen phosphate dihydrate Ph.Eur.	3.90 mg/ml
Sodium methyl parahydroxybenzoate Ph.Eur.	2.00 mg/ml
Sodium propyl parahydroxybenzoate Ph.Eur.	0.20 mg/ml
Xanthan gum Ph.Eur.	5.50 mg/ml
Glycerol Ph.Eur	130.00 mg/ml
Sodium Hydroxide	q.s
Hydrochloric Acid	q.s
Purified water Ph.Eur.	to 1ml

5 NAME AND ADDRESS OF MANUFACTURER(s)

Manufacturer responsible for the active substance
Clozapine
Medichem SA
Poligono Industriale de Celra
17460 Celra
Gerona
Spain

Manufacturer responsible for manufacture and assembly
Douglas Pharmaceuticals Ltd
Central Park Drive
Lincoln
PO Box 45027
Auckland
New Zealand

Manufacturer responsible for batch release
Merz Pharma UK Ltd
260 Centennial Park
Elstree Hill South
Elstree
Herts WD6 3 SR
UK

6 METHOD OF SALE OR SUPPLY

Product subject to prescription which may not be renewed (A)
Supply through pharmacies only

7 METHOD OF SALES PROMOTION

Promotion to healthcare professionals only

8 SPECIAL LABELLING OR LEAFLET REQUIREMENTS

Label

None

Leaflet

None

9 SPECIAL CONDITIONS

DENZAPINE Official Recommendations:
DENZAPINE is associated with a specific risk of agranulocytosis. Any adverse haematological effects should be notified to the Irish Medicines Board.
Intrinsic to Denzapine therapy is enrolment with and monitoring by the DENZAPINE Monitoring Service (DMS), based at:
Denzapine Monitoring Service
Merz Pharma UK Ltd., 260 Centennial Park, Elstree South, Elstree, Hertfordshire WD6 3SR, UK.
The DMS database embodies tightly controlled post-marketing surveillance and ensures the safe use of DENZAPINE in registered patients. Features of the DMS which are of fundamental importance to patient safety include the following:
Psychiatrists who wish to prescribe DENZAPINE must be registered with the DMS.
Pharmacists dispensing DENZAPINE must be registered with the DMS.
Patients to receive DENZAPINE must be enrolled with the DMS. They must undergo pre-treatment screening, as well as subsequent haematological tests. These will be weekly initially, then may become fortnightly after a period of 18 weeks.
DENZAPINE may be given to patients only if blood screening confirms that the subject's levels of white blood cells and neutrophils fall with in pre-set safety margins.

Supply of DENZAPINE to a patient is given only if the DMS is satisfied that continued haematology results are satisfactory.
Monitoring of patients receiving DENZAPINE continues for the duration of treatment, and for four weeks after a patient has stopped treatment.
Local independent expert haematological support should be utilised where general advice is required, and where specific assistance is deemed beneficial, in addition to the haematological expertise integral to the DMS.
DENZAPINE therapy is initiated in hospital and, following discharge of patients, monitoring still remains under the direct care of the psychiatric unit.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Denzapine 50mg/ml Oral Suspension

DENZAPINE can cause agranulocytosis. Its use should be limited to patients:

- **with schizophrenia who are non-responsive to or intolerant of antipsychotic drug treatment, or with psychosis in Parkinson's disease when other treatment strategies have failed (see point 4.1)**
- **who have initially normal leukocyte findings (white blood cell count of >3500/mm^3 (3.5 x 10^9 /L), and an absolute neutrophil count (ANC) of >2000/mm^3 (2.0 x 10^9 /L)), and**
- **in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of DENZAPINE**

Prescribing physicians should comply with the required safety measures. At each consultation, a patient receiving DENZAPINE should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

DENZAPINE must be dispensed under strict medical supervision in accordance with official recommendations.

Myocarditis

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely.

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction.

If myocarditis or cardiomyopathy are suspected, DENZAPINE treatment should be promptly stopped and the patient immediately referred to a cardiologist.
Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of oral suspension contains 50 mg of Clozapine.

Excipients:

Each 1ml of oral suspension also contains 150mg sorbitol, 2mg sodium methyl parahydroxybenzoate and 0.2mg sodium propyl parahydroxybenzoate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

Free-flowing yellow suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

DENZAPINE is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

DENZAPINE is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

4.2 Posology and method of administration

Method of Administration – Oral

When first dispensed or when there is visible settling of the suspension, Clozapine Suspension should be shaken well for 90 seconds before being dispensed or used. In all other instances the bottle should be shaken for 10 seconds before a dose is dispensed.

If dilution is required, the suspension may be mixed with water but not fruit juice or any other form of liquid.

The dosage must be adjusted individually. For each patient the lowest effective dose should be used.

Initiation of DENZAPINE treatment must be restricted to those patients with a WBC count over $3500/mm^3$ ($3.5 \times 10^9/L$) and an absolute neutrophil count (ANC) greater than $2000/mm^3$ ($2.0 \times 10^9/L$) within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacodynamic and pharmacokinetic interactions with DENZAPINE, such as benzodiazepines or selective serotonin re-uptake inhibitors (see section 4.5 **Interaction with other medicinal products and other forms of interaction**).

The following dosages are recommended:

Treatment-resistant schizophrenic patients

Starting therapy

12.5 mg (0.25 ml of suspension) once or twice on the first day, followed by 25 mg (0.5 ml of suspension) or 50mg (1.0 ml of suspension) on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50 mg (0.5 ml to 1.0 ml of suspension) in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg (1.0 ml to 2.0 ml of suspension) at half-weekly or, preferably, weekly intervals.

Use in children
Not Recommended in Children.

Use in the elderly
Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg/day.

Therapeutic dose range
In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day (4 ml to 9 ml/day) given in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime. For maintenance dose, see below.

Maximum dose
To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (i.e. not exceeding 100 mg or 2 ml) are permissible up to 900 mg/day (18 ml). The possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day (9 ml/day) must be borne in mind.

Maintenance dose
After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.

Ending therapy
In the event of planned termination of DENZAPINE therapy, a gradual reduction in dose over a 1- to 2-week period is recommended. If abrupt discontinuation is necessary (e.g. because of leucopoenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhoea.

Re-starting therapy
In patients in whom the interval since the last dose of DENZAPINE suspension exceeds 2 days, treatment should be re-initiated with 12.5 mg (0.25 ml) given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see section 4.4 **Special warnings and precautions for use**), but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution.

Switching from a previous antipsychotic therapy to DENZAPINE
It is generally recommended that DENZAPINE should not be used in combination with other antipsychotics, including depot preparations, which may have a myelosuppressive effect. When DENZAPINE therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.

Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed

The starting dose must not exceed 12.5 mg/day (0.25 ml) taken in the evening. Subsequent dose increases must be by 12.5 mg increments (0.25 ml), with a maximum of two increments a week up to a maximum of 50 mg (1 ml), a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

The mean effective dose is usually between 25 and 37.5 mg/day (0.5 and 0.75 ml/day). In the event that treatment for at least one week with a dose of 50 mg (1 ml) fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week (0.25 ml/week).

The dose of 50 mg/day (1 ml/day) should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day (2 ml/day) must never be exceeded.

Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.

When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, DENZAPINE dosage may be increased by increments of 12.5 mg/week (0.25 ml/week) up to a maximum of 100 mg/day (2 ml/day), taken in one or two divided doses (see above).

Ending therapy: A gradual reduction in dose by steps of 12.5 mg (0.25 ml) over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis as indicated in section 4.4 **(Special warnings and precautions for use)**. In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with known or suspected hereditary problems of fructose intolerance should not take this oral suspension
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- History of DENZAPINE -induced agranulocytosis.
- Impaired bone marrow function.
- Uncontrolled epilepsy.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS depression of any cause.
- Severe renal or cardiac disorders (e.g. myocarditis).
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
- Paralytic ileus.
- DENZAPINE treatment must not be started concurrently with drugs known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.

4.4 Special warnings and precautions for use

Precautions

DENZAPINE can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of WBC counts and ANC monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations.

Because of the risks associated with DENZAPINE, its use is limited to patients in whom therapy is indicated as set out in section 4.1 **(Therapeutic indications)** and:

- who have initially normal leukocyte findings (WBC count greater than 3500/mm^3 (3.5 x 10^9/L) and ANC above 2000/mm^3 (2.0 x 10^9/L), and
- in whom regular WBC counts and ANC can be performed weekly for the first 18 weeks and at least 4-week intervals thereafter. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of DENZAPINE.

Before initiating clozapine therapy patients should have a blood test (see "agranulocytosis") and a history and physical examination.

Patients with history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks (see Section 4.3). The treating physician should consider performing a pre-treatment ECG. Caution should be exercised in patients with cardiovascular disease or a family history of QT prolongation.

The concomitant administration of neuroleptic medicines should be avoided.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. DENZAPINE should be used with caution in patients with risk factors for stroke.

Prescribing physicians should comply fully with the required safety measures.

- Prior to treatment initiation, physicians must ensure, to the best of their knowledge, that the patient has not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation. Prescriptions should not be issued for periods longer than the interval between two blood counts.

- Immediate discontinuation of DENZAPINE is mandatory if either the WBC count is less than 3000/mm^3 (3.0 x 10^9 /L) or the ANC is less than 1500/mm^3 (1.5 x 10^9 /L) at any time during DENZAPINE treatment. Patients in whom DENZAPINE has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to DENZAPINE.

- At each consultation, a patient receiving DENZAPINE should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately. Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

- Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting DENZAPINE

- Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may be started on DENZAPINE with the agreement haematologist.

WBC Counts and ANC Monitoring

WBC and differential blood counts must be performed within 10 days prior to initiating DENZAPINE treatment to ensure that only patients with normal WBC counts (WBC count greater than 3500/mm^3 (3.5 x 10^9/L) and ANC above 2000/mm^3 (2.0 x 10^9/L)) will receive the drug. After the start of DENZAPINE treatment the WBC count and ANC must be monitored weekly for the first 18 weeks, and at least at four-week intervals thereafter.

Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of DENZAPINE or until haematological recovery has occurred (see below Low WBC count/ANC). At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count/ANC

If, during DENZAPINE therapy, either the WBC count falls to between 3500/mm^3 (3.5 x 10^9/L) and 3000/mm^3 (3.0 x 10^9/L) or the ANC falls to between 2000/mm^3 (2.0 x 10^9/L) and 1500/mm^3 (1.5 x 10^9/L), haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3000-3500/mm^3 (3.0 - 3.5 x 10^9/L) and 1500 - 2000/mm^3 (1.5 - 2.0 x 10^9/L), respectively, or higher.

Immediate discontinuation of DENZAPINE treatment is mandatory if either the WBC count is less than 3000/mm^3 (3.0 x 10^9/L) or the ANC is less than 1500/mm^3 (1.5 x 10^9/L) during DENZAPINE treatment. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, DENZAPINE should be discontinued after the first blood count.

Following discontinuation of DENZAPINE, haematological evaluation is required until haematological recovery has occurred.

Blood cell count		Action required
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
>3500 (3.5 x 10^9)	>2000 (2.0 x 10^9)	Continue DENZAPINE treatment
3000- 3500 (3.0 x 10^9 - 3.5 x 10^9)	1500-2000 (1.5 x 10^9 - 2.0 x 10^9)	Continue DENZAPINE treatment, sample blood twice weekly until counts stabilise or increase
<3000 (< 3.0 x 10^9)	< 1500 (< 1.5 x 10^9)	Immediately stop DENZAPINE treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

If DENZAPINE has been withdrawn and either a further drop in the WBC count below 2000/mm^3 (2.0 x 10^9/L) occurs or the ANC falls below 1000/mm^3 (1.0 x 10^9/L), the management of this condition must be guided by an experienced haematologist.

Discontinuation of therapy for haematological reasons

Patients in whom DENZAPINE has been discontinued as a result of either WBC or ANC deficiencies (see above) must not be re-exposed to DENZAPINE.

Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged in the future.

Discontinuation of therapy for other reasons

Patients who have been on DENZAPINE for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If DENZAPINE treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment and the dose should be re-titrated (see section **4.2 Posology and method of administration**).

Other precautions

In the event of **eosinophilia**, discontinuation of DENZAPINE is recommended if the eosinophil count rises above 3000/mm^3 (3.0 x 10^9/L); therapy should be restarted only after the eosinophil count has fallen below 1000/mm^3 (1.0 x 10^9/L).

In the event of **thrombocytopenia**, discontinuation of DENZAPINE therapy is recommended if the platelet count falls below 50 000/mm^3 (50 x 10^9/L).

Orthostatic hypotension, with or without syncope, can occur during DENZAPINE treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur with concurrent use of benzodiazepines or any other psychotropic agent (see section **4.5 Interaction with other medicinal products and other forms of interaction**) and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Therefore, patients commencing DENZAPINE treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

Analysis of safety databases suggests that the use of clozapine is associated with an increased risk of **myocarditis** especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal.

Pericarditis/pericardial effusion and **cardiomyopathy** have also been reported in association with clozapine use; these reports also include fatalities. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy are suspected, DENZAPINE treatment should be promptly stopped and the patient immediately referred to a cardiologist.

Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to DENZAPINE.

Patients with a history of epilepsy should be closely observed during DENZAPINE therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced (see section **4.2 Posology and method of administration**) and, if necessary, an anti-convulsant treatment should be initiated.

Patients with stable pre-existing liver disorders may receive DENZAPINE, but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible **liver dysfunction**, such as nausea, vomiting and/or anorexia, develop during DENZAPINE therapy. If the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with DENZAPINE must be discontinued. It may be resumed (see **"Re-starting therapy"** under section 4.2) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of the drug.

DENZAPINE exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow-angle glaucoma**. Probably on account of its anticholinergic properties, clozapine has been associated with varying degrees of **impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction**, **faecal impaction** and **paralytic ileus** (see section **4.8 Undesirable effects**). On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.

During DENZAPINE therapy, patients may experience transient **temperature elevations** above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of **neuroleptic malignant syndrome** (NMS) must be considered.

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined. Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycaemia, some of which have been fatal. When follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its reoccurrence. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.

Since DENZAPINE may be associated with **thromboembolism**, immobilisation of patients should be avoided.

Use in the elderly

Initiation of treatment in the elderly is recommended at a lower dose (see section **4.2 Posology and method of administration**).

Orthostatic hypotension can occur with DENZAPINE treatment and there have been reports of tachycardia, which may be sustained. Elderly patients, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Elderly patients may also be particularly susceptible to the anticholinergic effects of DENZAPINE, such as urinary retention and constipation.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindication of concomitant use

Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with DENZAPINE (see section **4.3 Contraindications**). These include co-trimoxazole, chloramphenicol, sulphonamides, pyrazolone analgesics e.g. phenylbutazone, penicillamine, carbamazepine or cytotoxic agents.

Long-acting depot antipsychotics (which have myelosuppressive potential) should not be used concurrently with DENZAPINE because these cannot be rapidly removed from the body in situations where this may be required, e.g. neutropenia (see section **4.3 Contraindications**).

Alcohol should not be used concomitantly with DENZAPINE due to possible potentiation of sedation.

Precautions including dose adjustment

DENZAPINE may enhance the central effects of CNS depressants such as narcotics, antihistamines, and benzodiazepines. Particular caution is advised when DENZAPINE therapy is initiated in patients who are receiving a benzodiazepine or any other psychotropic drug. These patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest. It is not clear whether cardiac or respiratory collapse can be prevented by dose adjustment.

Because of the possibility of additive effects, caution is essential in the concomitant administration of drugs possessing anticholinergic, hypotensive, or respiratory depressant effects.

Owing to its anti-α-adrenergic properties, DENZAPINE may reduce the blood-pressure-increasing effect of norepinephrine or other predominantly α-adrenergic agents and reverse the pressor effect of epinephrine.

Concomitant administration of drugs known to inhibit the activity of some cytochrome P450 isozymes may increase the levels of clozapine, and the dose of clozapine may need to be reduced to prevent undesirable effects. This is more important for CYP 1A2 inhibitors such as caffeine (see below) and the selective serotonin reuptake inhibitors fluvoxamine and (more controversial) paroxetine. Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine and to a lesser degree sertraline are CYP 2D6 inhibitors and, as a consequence, major pharmacokinetic interactions with clozapine are less likely. Similarly, pharmacokinetic interactions with CYP 3A4 inhibitors such as azole antimycotics, cimetidine, erythromycin, and protease inhibitors are unlikely, although some have been reported. Because the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period, dosage changes of clozapine may be necessary when there is a change in caffeine-drinking habit. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated.

Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine, leading to reduced efficacy. Drugs known to induce the activity of cytochrome P450 enzymes and with reported interactions with clozapine include, for instance, carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppresive potential), phenytoin and rifampicin. Known inducers of CYP1A2 such as omeprazole, may lead to decreased clozapine levels. The potential for reduced efficacy of clozapine should be considered when it is used in combination with these drugs.

Others

Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

Concomitant use of clozapine with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including Torsades de pointes. Therefore concomitant use of these products is not recommended.

Examples include certain antiarrhythmics, such as those of Class IA(such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin, moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide, sertindole and haloperidol), certain antihistamines (such as terfenadine), cisapride, bretylium and certain antimalarials such as quinine and mefloquine. This list is not comprehensive.

Concurrent use of drugs causing electrolyte imbalance is not recommended. Diuretics, in particular those causing hypokalemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where DENZAPINE was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Caution is called for in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of the cytochrome P450 isozymes. With tricyclic antidepressants, phenothiazines and type I_C anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

An outline of drug interactions believed to be most important with DENZAPINE is given in Table 1 below (this is not an exhaustive list).

Table 1: Reference to the most common drug interactions with DENZAPINE

Drug	Interactions	Comments
Bone marrow suppressants (e.g. carbamazapine, chloramphenicol, sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression	DENZAPINE **should not be used** concomitantly with other agents having a well known potential to suppress bone marrow function (see Section **4.3 Contraindications**)
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest	Whilst the occurrence is rare, caution is advised when using these drugs together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when DENZAPINE is added to an established benzodiazepine regimen.

Anticholinergics	DENZAPINE potentiates the action of these drugs through additive anticholinergic activity	Observe patients for anticholinergic side – effects, e.g. constipation, especially when using to help control hypersallvation
Antihypertensives	DENZAPINE can potentiate the hypotensive effects of these drugs due to its sympathomimetic antagonistic effects	Caution is advised if DENZAPINE is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these drugs	Caution is advised if DENZAPINE is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery
Highly protein bound drugs (e.g. warfarin and digoxin)	DENZAPINE may cause an increase in plasma concentration of these drugs due to displacement from plasma proteins	Patients should be monitored for the occurrence of side effects associated with these drugs, and doses of the protein bound drug adjusted, if necessary
Phenytoin	Addition of phenytoin to DENZAPINE drug regimen may cause a decrease in the clozapine plasma concentrations	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS)	Observe for signs and symptoms of NMS

4.6 Pregnancy and lactation

Pregnancy

For clozapine, there are only limited clinical data on exposed pregnancies. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see 5.3). Caution should be exercised when prescribing to pregnant women.

Lactation

Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving DENZAPINE should not breast-feed.

Women of child-bearing potential

A return to normal menstruation may occur as a result of switching from other antipsychotics to DENZAPINE. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

4.7 Effects on ability to drive and use machines

Owing to the ability of DENZAPINE to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

4.8 Undesirable effects

For the most part, the adverse event profile of clozapine is predictable from its pharmacological properties. An important exception is its propensity to cause agranulocytosis (see section **4.4 Special warnings and precautions for use**). Because of this risk, its use is restricted to treatment-resistant schizophrenia and psychosis occurring during the course of Parkinson's disease in cases where standard treatment has failed. While blood monitoring is an essential part of the care of patients receiving clozapine, the physician should be aware of other rare but serious adverse events, which may be diagnosed in the early stages only by careful observation and questioning of the patient in order to prevent morbidity and mortality.

Blood and lymphatic system

Development of granulocytopenia and agranulocytosis is a risk inherent to DENZAPINE treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of the drug is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory (see section **4.4 Special warnings and precautions for use**). Table 2 below summarises the estimated incidence of agranulocytosis for each DENZAPINE treatment period.

Table 2: Estimated incidence of agranulocytosis[1]

Treatment period	Incidence of agranulocytosis per 100,000 person-weeks[2] of observation
Weeks 0 - 18	32.0
Weeks 19 - 52	2.3
Weeks 53 and higher	1.8

[1] From the UK Patient Monitoring Service lifetime registry experience between 1989 and 2001.

[2] Person-time is the sum of individual units of time that the patients in the registry have been exposed to clozapine before experiencing agranulocytosis. For example, 100,000 person-weeks could be observed in 1,000 patients who were in the registry for 100 weeks (100*1000 = 100,000), or in 200 patients who were in the registry for 500 weeks (200*500 = 100,000) before experiencing agranulocytosis.

The cumulative incidence of agranulocytosis in the UK since monitoring began is (0 - 11.6 years between 1989 and 2001) is 0.78 %. The majority of cases (approximately 70 %) occur within the first 18 weeks of treatment.

Metabolic and Nutritional Disorders

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported in patients on clozapine treatment with no prior history of hyperglycaemia. Glucose levels normalised in most patients after discontinuation of clozapine and in a few cases hyperglycaemia recurred when treatment was reinitiated. Although most patients had risk factors for non-insulin-dependent diabetes mellitus, hyperglycaemia has also been documented in patients with no known risk factors (see section **4.4. Special warnings and precautions for use**).

Nervous System Disorders

The very common adverse events observed include drowsiness/sedation, and dizziness.

DENZAPINE can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures. These symptoms are more likely to occur with rapid dose increases and in patients with pre-existing epilepsy. In such cases the dose should be reduced and, if necessary, anticonvulsant treatment initiated. Carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsant drugs the possibility of a pharmacokinetic interaction should be considered. In rare cases, patients treated with DENZAPINE may experience delirium.

Very rarely, tardive dyskinesia has been reported in patients on clozapine who had been treated with other antipsychotic agents. Patients in whom tardive dyskinesia developed with other antipsychotics have improved on clozapine.

Cardiac Disorders

Tachycardia and postural hypotension with or without syncope may occur, especially in the initial weeks of treatment. The prevalence and severity of hypotension is influenced by the rate and magnitude of dose titration. Circulatory collapse as a result of profound hypotension, in particular related to aggressive titration of the drug, with the possible serious consequences of cardiac or pulmonary arrest, has been reported with clozapine.

A minority of clozapine-treated patients experience ECG changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which normalise after discontinuation of clozapine. The clinical significance of these changes is unclear. However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered.

Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion and myocarditis have been reported, some of which have been fatal. The majority of the cases of myocarditis occurred within the first 2 months of initiation of therapy with clozapine. Cardiomyopathy generally occurred later in the treatment.

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14 %) and pericarditis/pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis.

Signs and symptoms of myocarditis or cardiomyopathy include persistent tachycardia at rest, palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms.

Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Such deaths have been reported very rarely in patients receiving clozapine.

Vascular Disorders

Rare cases of thromboembolism have been reported.

Respiratory System

Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse (see sections **4.4 Special warnings and precautions for use** and **4.5 Interaction with other medicinal products and other forms of interaction**).

Gastrointestinal System

Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rarely ileus may occur (see section **4.4 Special warnings and precautions for use**). Rarely DENZAPINE treatment may be associated with dysphagia. Aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

Hepatobiliary Disorders

Transient, asymptomatic elevations of liver enzymes and rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, DENZAPINE should be discontinued (see section **4.4. Special warnings and precautions for use**). In rare cases, acute pancreatitis has been reported.

Renal Disorders

Isolated cases of acute interstitial nephritis have been reported in association with DENZAPINE therapy.

Reproductive and Breast Disorders

Very rare reports of priapism have been received.

General Disorders

Cases of neuroleptic malignant syndrome (NMS) have been reported in patients receiving clozapine either alone or in combination with lithium or other CNS-active agents.

The table below (Table 3) summarises the adverse reactions accumulated from reports made spontaneously and during clinical studies.

Table 3: Treatment-Emergent Adverse Experience Frequency Estimate from Spontaneous and Clinical Trial Reports
Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), including isolated reports.

Blood and lymphatic system disorders	
Common	Leucopoenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon	Agranulocytosis
Rare	Anaemia
Very rare	Thrombocytopenia Thrombocythaemia

Metabolism and nutrition disorders	
Common	Weight gain
Rare	Impaired glucose tolerance, diabetes mellitus
Very rare	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia
Psychiatric disorders	
Rare	Restlessness, agitation
Nervous system disorders	
Very common	Drowsiness/sedation, dizziness
Common	Blurred vision, headache, tremor, rigidity, akathisia, extra pyramidal symptoms, seizures/convulsions/myoclonic jerks
Cardiac Disorders	
Very common	Tachycardia
Common	ECG changes
Rare	Circulatory collapse, Ventricular arrhythmias (VF, VT), myocarditis, pericarditis/pericardial effusion
Very rare	Cardiomyopathy, cardiac arrest, QT prolongation, Torsades de pointes
Vascular Disorders	
Common	Hypertension, postural hypotension, syncope
Rare	Thromboembolism
Respiratory disorders	
Rare	Aspiration in ingested food
Very rare	Respiratory depression/arrest
Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, anorexia, dry mouth
Rare	Dysphagia
Very rare	Parotid gland enlargement, intestinal obstruction/paralytic ileus/faecal impaction
Hepatobiliary disorders	
Common	Elevated liver enzymes
Rare	Hepatitis, cholestatic jaundice, pancreatitis
Very rare	Fulminant hepatic necrosis

Skin and subcutaneous tissue disorders	
Very rare	Skin reactions
Renal and urinary disorders	
Common	Urinary incontinence, urinary retention
Very rare	Interstitial nephritis
General disorders	
Common	Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation
Uncommon	Neuroleptic malignant syndrome
Very rare	Sudden unexplained death
Investigations	
Rare	Increased CPK

4.9 Overdose

In cases of acute intentional or accidental clozapine overdosage for which information on the outcome is available, mortality to date is about 12 %. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg (40 ml). There have been reports of patients recovering from an overdose in excess of 10 000 mg (200 ml). However, in a few adult individuals, primarily those not previously exposed to clozapine, the ingestion of doses as low as 400 mg (8 ml) led to life-threatening comatose conditions and, in one case, to death. In young children, the intake of 50 to 200 mg (1 to 4 ml) resulted in strong sedation or coma without being lethal.

Signs and symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extra pyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment

Gastric lavage and/or administration of activated charcoal within the first 6 hours after the ingestion of the drug. Peritoneal dialysis and haemodialysis are unlikely to be effective. Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect.

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotic agent (ATC code NO5A H02)

Clozapine has been shown to be an antipsychotic agent that is different from classic antipsychotics.

In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine-receptor-blocking activity at D_1, D_2, D_3 and D_5 receptors, but shows high potency for the D_4 receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinically clozapine produces rapid and marked sedation and exerts antipsychotic effects in schizophrenic patients resistant to other drug treatment. In such cases, clozapine has proven effective in relieving both positive and negative schizophrenic symptoms mainly in short-term trials. In an open clinical trial performed in 319 treatment resistant patients treated for 12 months, a clinically relevant improvement was observed in 37 % of patients within the first week of treatment and in an additional 44 % by the end of 12 months. The improvement was defined as about 20 % reduction from baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.

Compared to classic antipsychotics, clozapine produces fewer major extra pyramidal reactions such as acute dystonia, parkinsonian-like side effects and akathisia. In contrast to classic antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence.

A potentially serious adverse reaction caused by clozapine therapy is granulocytopenia and agranulocytosis occurring at an estimated incidence of 3 % and 0.7 %, respectively. In view of this risk, the use of DENZAPINE should be limited to patients who are treatment-resistant or patients with psychosis in Parkinson's disease when other treatment strategies have failed (see section **4.1 Therapeutic indications**) and in whom regular haematological examinations can be performed (see sections **4.4 Special warnings and precautions for use** and 4.8 **Undesirable effects**).

5.2 Pharmacokinetic properties

The absorption of orally administered DENZAPINE is 90 to 95 %; neither the rate nor the extent of absorption is influenced by food.

Clozapine is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50 to 60 %. In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 l/kg. Clozapine is approximately 95 % bound to plasma proteins. Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg (1.5 ml) the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg (1.5 ml) for at least 7 days. Dosage increases from 37.5 mg to 75 mg (0.75 to 1.5 ml) and 150 mg (3 ml) given twice daily were found to result during steady state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC), and in the peak and minimum plasma concentrations.

Clozapine is almost completely metabolised before excretion. Of the main metabolites only the demethyl metabolite was found to be active. Its pharmacologieal actions resemble those of clozapine, but are considerably weaker and of short duration. Only trace amounts of unchanged drug are detected in the urine and faeces, approximately 50 % of the administered dose being excreted as metabolites in the urine and 30 % in the faeces.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential (for reproductive toxicity, see section 4.6). There are no preclinical data of any relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E422)
Sodium dihydrogen phosphate dihydrate (E339(i))
Sorbitol (E420)
Xanthan gum (E415)

Povidone (E1201)
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)
Hydrochloric acid (for pH adjustment) (E507)
Sodium hydroxide (for pH adjustment) (E524)
Water, Purified

6.2 Incompatibilities

Clozapine Suspension is not compatible with orange juice. Therefore it is recommended that if Clozapine Suspension is to be mixed with a beverage, only water is to be used.

6.3 Shelf Life

Unopened: 2 years
In-use shelf life: 90 days after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottle containing 100 ml of suspension.
The bottle is fitted with a white, polypropylene, round child-resistant, tamper-evident screw cap containing a LDPE foam liner.
The filled and sealed bottle is packed into a carton along with a bottle adaptor and two graduated oral dispensers (1 x 1 ml oral dispenser and 1 x 10 ml oral dispenser) for dispensing and administration of the suspension.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Merz Pharma UK Ltd
260 Centennial Park
Elstree Hill South
Elstree, Hertfordshire
WD6 3SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT